NEUROLOGICAL ASPECTS OF THE AVITAMINOSES, WITH SPECIAL REFERENCE TO THE PERIPHERAL NERVOUS SYSTEM

BY

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Avitaminosis and the Nervous System

It is an interesting fact that the particular field of study of avitaminosis and the nervous system, opened up by Eijkman (1) so long ago as 1896 and developed by Grijns (2), Schaumann (3), Vedder (4) and many others, still holds pride of place at the present day. At that time, experimental work in the laboratory on polyneuritis gallinarum and clinical investigation on human beri-beri were carried on side by side and, as a result, it is now known that vitamin B_1 (aneurin) has a preventive and curative action in both these conditions. Clinical work has since established the curative effect of the same vitamin in alcoholic and possibly in some other forms of polyneuritis and in Korsakoff's psychosis. As so often happens in medical science, clinical knowledge and control of nervous disease have not continued to advance side by side with the fundamental knowledge gained in the laboratory and we still do not clearly understand what is the true cause of the symptoms of, and how vitamin B_1 acts in, some of these diseases.

Thus, while it is true that all the earlier work established the dominant role of vitamin B_1 deficiency in polyneuritis gallinarum and beri-beri, the fact remains that there is still no clear evidence that an uncomplicated vitamin B_1 deficiency ever causes in mammals or birds the degree of degeneration in the peripheral nerves that is found in beri-beri and other forms of polyneuritis in man. Many investigations have been made on this point and, although the evidence is not conclusive, the general weight of opinion is against the view that vitamin B_1 deficiency in itself causes in animals a multiple peripheral neuritis which can be demonstrated histologically. That is also my experience. It is commonly said that the failure to produce peripheral neuritis in rats and birds is due to the fact that the experiments have usually been too acute in nature and that a partial deficiency lasting over a long period would be more successful. It is however,

very difficult to produce in such animals a prolonged state of vitamin B_1 deficiency for, if there is any deficiency at all, the animals, in particular rats and birds, usually show great incoordination and die rapidly. Administration of small amounts of vitamin B_1 to such animals generally brings about rapid recovery. The animals do not show the severe nerve degeneration of polyneuritis, and their rapid recovery to normal precludes the possibility of extensive organic change in the nervous system. Some evidence of the production of definite degeneration of peripheral nerves by vitamin B_1 deficiency in the case of dogs has been obtained by Cowgill (5). There are also a certain number of observations which seem to point to the possibility of a central lesion in animals suffering from vitamin B_1 deficiency: Prickett (6) in rats, Vedder and Clark (7) in fowls, obtained such changes, while Gildea, Kattwinkel and Castle (8) produced a condition in dogs resembling combined systemic disease in man by diets deficient in vitamin B_1.

Engel and Phillips (9) have recently endeavoured to bridge the gap between the laboratory and clinical results as regards polyneuritis and believe from their animal experiments that vitamin B_1 deficiency makes an excessive call on other vitamins such as vitamin A and riboflavine and that a combined deficiency is really responsible for the organic changes in peripheral nerves. They say that these degenerative changes can be prevented even in vitamin B_1 deficiency if the dietetic vitamin A and riboflavine are sufficient in amount.

Recent work on alcoholic polyneuritis and its cure by vitamin B_1 also suggests a possible connecting link between the clinical observations and the failure to produce demyelination of peripheral nerves in experimental animals. Wechsler (10) and others have shown clearly that, even if a patient with alcoholic neuritis continues to consume a large amount of alcohol, large doses of vitamin B_1 will cure the condition. It may be, therefore, that whereas neither B_1 deficiency nor alcohol can itself produce the degenerative changes in nerves, a combination of both can do so. In the development of beri-beri there may also be an additional factor at work acting in the same way as alcohol in alcoholic polyneuritis. If this is so, we are strangely near Eijkman's original view of the aetiology of the disease. The curative effect of large amounts of vitamin B_1 on polyneuritis, even when alcohol is being consumed, shows that the activity of this vitamin in the body is greatly reduced by alcohol, either absolutely because of a diminished absorption from the alimentary canal

or relatively because a much greater demand on vitamin B_1 activity in the body is created by alcohol.

When we come to the question of how vitamin B_1 acts on the nervous system, and why its absence leads to abnormality of function, laboratory studies have placed the subject on surer ground, although it is doubtful whether the clinician is yet in a position from his own practical experience of nerve disease in man to appreciate this advance in knowledge. For, whereas the laboratory worker can now understand why his vitamin B_1 deficient animals recover immediately on administering this substance, the type of human disease that responds to vitamin B_1 administration is of a chronic nature and recovery is usually slow. It has now been established by Peters (11) and his colleagues at Oxford that the essential part played by vitamin B_1 in brain and nerve tissue physiology and indeed in that of all other tissues, especially that of the heart and kidney, is to control carbohydrate metabolism. Any tissue specially susceptible to abnormal carbohydrate metabolism, such as the brain and nervous tissue, or the heart and kidney, is therefore rapidly upset by vitamin B_1 deficiency. Working in vitro with the brain tissue of birds deficient in vitamin B_1, Peters and his colleagues found that oxidation of dextrose after passing through the lactic acid stage to pyruvic acid, stopped but proceeded if vitamin B_1 was added. In other words, the oxidation of pyruvate by brain tissue required the presence of vitamin B_1. The importance of these results was emphasised by the discovery of Thompson and Johnson (12) that the blood of pigeons and rats suffering from vitamin B_1 deficiency contained pyruvate and that of Platt and Lu (13) who found the same substance in the blood of human cases of beri-beri.

We are still not clear how the further identification of Lohmann and Schuster (14) of co-carboxylase with vitamin B_1 pyrophosphate will affect the story of carbohydrate in the brain. Co-carboxylase was first isolated from yeast and found to be the co-enzyme necessary for the conversion of pyruvic acid to acetaldehyde and carbon dioxide. It is true that there is a large decrease in the co-carboxylase in the brain of pigeons suffering from vitamin B_1 deficiency and it is probable that the active form of vitamin B_1 in this tissue when normal is phosphorylated. On the other hand, it appears that the evidence at present available shows that vitamin B_1 itself has a more powerful effect in vitro of

promoting carbohydrate oxidation in brain tissue than co-carboxylase, a discrepancy which Peters points out is possibly due to the fact that co-carboxylase is isolated from yeast and it may well be that the phosphorylated compound in animal tissue is not identical. This subject is being actively investigated and will undoubtedly become clearer in the near future. It is, however, established beyond doubt that vitamin B_1 deficiency prevents proper nervous function, largely because it interferes with carbohydrate oxidation, a type of metabolic process upon which nervous tissue is very dependent.

Nicotinic Acid

The recent establishment of nicotinic acid as the pellagra preventing factor and the undoubted fact that pellagra is often but not always associated with both central and peripheral lesions of the nervous system require consideration to be given to the possibility that nicotinic acid plays a part in nerve physiology and pathology. Nerve lesions found in pellagra include polyneuritis, changes in Betz cells and in motor cells of the cord and degeneration of the medullary sheaths of the posterior column and of the direct and crossed pyramidal tracts. At the present time there is no experimental and but little clinical evidence that deficiency of nicotinic acid is responsible for nerve degenerative changes. It is of interest, however, to note the beneficial effects of nicotinic acid on certain psychotic states associated with malnutrition recently reported by Cleckley, Sydenstricker and Geeslin (15). Although pellagra is undoubtedly primarily due to a deficient intake of nicotinic acid, dietetic conditions responsible for its development are often more complicated than this, as indeed is the case in beri-beri and other deficiency diseases. For instance, alcoholism is often an associated factor in the development of pellagra and it may be that vitamin B_1 deficiency is also an essential cause of the irregular incidence of polyneuritis and lesions of the central nervous system often seen in pellagra.

Vitamin B_6

The action of a probable deficiency of this vitamin recently described by Chick, Macrae, Martin and Martin (16) in pigs, and by Fouts, Helmer, Lepkovsky and Jukes (17) in puppies suggests that it may be of importance from the point of view of the nervous system. The first of these groups of authors found that pigs deprived of a certain eluate fraction prepared from yeast which contained vitamin B_6 developed epileptic fits and that further attacks were prevented when this fraction was added to the diet.

The second group of authors reported the development of convulsions in puppies when deprived of a liver fraction similar to the yeast fraction used by Chick et al.

Now that the constitution of vitamin B_6 has been found by Kuhn, Wendt and Westphal (18) to be 2-methyl-3-hydroxy-4:5-di (hydroxymethyl) piridine and the substance has been synthesised by Harris and Folker (19), it ought to be possible to get clear evidence as to whether it is this substance or another which is responsible for the specific disorder of the nervous system.

Anahaemin (the anti-anaemia substance of liver)

Although the development of combined systemic disease of the cord in association with pernicious anaemia may not be classed as an avitaminosis, the relationship is so close as to merit a passing reference. Clinical experience seems to point to the fact that the substance in the liver which brings back the blood picture of pernicious anaemia to normal is also the substance which, in higher dosage, stops the advance of the degenerative changes found in sub-acute combined degeneration and in early cases has curative effects. This is a matter of great scientific interest as well as being of outstanding clinical importance, since there is no reason to believe that the anaemia in itself is the cause of the nerve degeneration changes, otherwise severe simple anaemia would be accompanied by the same nervous lesions. There is still some disagreement as to whether the curative factor obtained from the liver in these diseases is a single chemical substance, but the powerful action of highly purified preparations, both in the control of pernicious anaemia and combined systemic disease, such as have been made by the method of Dakin and West (20), suggests the identity of the agent affecting both the blood and nerve conditions.

Vitamin A

I wish now to turn to an aspect of the effect of nutritional deficiencies on the nervous system with which I am more familiar. I refer to the effect of vitamin A deficiency. If vitamin A and carotene are deficient in the diets of young animals such as dogs and rabbits, especially if the cereal content of the diet is high, extensive nerve degeneration develops both in the central and peripheral nervous systems (21). Whole tracts of the cord may

practically disappear, within a few months of dieting. In the central nervous system there is no great neuroglial reaction and no evidence of inflammatory change.

In these animal experiments, generally speaking, it is the afferent side of the nervous system which is specially affected and degenerative changes have only been definitely found in the first and second neurones, although there are indications in some of the advanced experiments that the third neurone may be affected. All the afferent nerves of the head except the vagus may suffer greatly. The motor cranial nerves inside the skull usually escape but some degeneration has occasionally been found in the third nerve. In the body, the same rule holds, the degeneration affecting primarily the dorsal root fibres, those of the anterior roots near the cord remaining normal except when the nutritional deficiency has been very prolonged. The affected fibres and tracts of the central nervous system are mostly ascending and include the dorsal and ventral spinal-cerebellar and dorsal and ventral spino-reticulo-thalamic tracts and the tracts of the dorsal columns. Some descending tracts suffer change, including the rubro-spinal and the dorsal longitudinal bundle and the vestibulo-spinal, all of which are associated with the mid-brain or medulla. The pyramidal tract generally escapes harm under these nutritional conditions.

Degenerative changes of various degrees are also seen in nerve cells. Such changes are found in the cells of the dorsal root and of the Gasserian ganglion in the case of the peripheral system and in the cells of Clark's column, Purkinje cells, those of the vestibular nucleus and many others in the central nervous system. In the mid-brain, the red nucleus, the dentate nucleus and sometimes the nucleus of the 3rd nerve occasionally show some abnormalities. Slight chromolysis of motor nerve cells of the anterior horn of the spinal cord is present in a few experimental animals, but no advanced changes have been noticed.

When these experimental facts were first described (22), I regarded them as comparable in some ways to those found in the so-called toxic degenerations, especially such conditions as convulsive ergotism, pellagra and lathyrism, which are known to be associated with restricted diets. Although there may still be a relationship between the experimental results described above and these clinical conditions, another factor

has recently come to light in this work, which demands a reorientation of attitude towards it (23). In the course of a closer investigation of the labyrinth and 8th nerve in young animals brought up on the vitamin A deficient diets described above, serial sections of the decalcified petrous portion of the temporal bone were cut and it was found that, associated with the disappearance of the cochlear and vestibular divisions of the nerve, there was much new bone formation, which was not present in the control animals on the same diet but receiving vitamin A or carotene in addition. This new bone was found in two positions, in each case of periosteal origin:-(a) in and near the modiolus itself; this bone presses on the nerves as they leave the cochlea and vestibule respectively; (b) around the internal auditory meatus, adjacent to the brain. This has the effect of placing the cochlea deeper into the capsule and of increasing the distance from the spiral and Scarpa's ganglia to the brain, a change which stretches and twists the nerve. Occasionally new bone can be seen in a third place, namely in the scala tympani at the basal whorl of the helix. Closer study of this condition leaves no doubt that the bone overgrowth in these places results finally in the destruction of the fibres of the 8th nerve. After the discovery of these facts, it was necessary to see whether all the nerve degenerative changes previously described could be attributed to bone overgrowth and the pressure and stretching effect of such growth on the nerve fibres or pressure on nerve cells resulting therefrom. While it is impossible as yet to say that this is the case, the following statement summarises in brief other pathological conditions which have come to light. It has been found, for instance, that with vitamin A deficiency there is an overgrowth of the petrous ridge and to some extent of the bone supporting the Gasserian ganglion. This results in compression both of the ganglion and of the fifth nerve centrally to the ganglion. The ganglion becomes elongated and the central root of the nerve bent. In an advanced case the enlargement of a small portion of bone partially plugged the foramen of the 5th nerve. Transverse sections of the optic nerve and the bone surrounding it also showed partial closure of the foramen and compression of the nerve by bone overgrowth. It is clear, therefore, that, so far as the brain is concerned, degenerative changes in the second, fifth and eighth nerves are all associated with bone overgrowth at the base of the skull, and it may well be that this bone overgrowth is responsible for the degenerative changes previously described in these nerves.

The whole base of the skull is affected by this bone overgrowth and the enlargement of the posterior and anterior clinoid processes has a compressing effect on the hypophysis. It may be added that not only is the base of the skull affected in this way but there is also some hypertrophy of the frontal, parietal and occipital bones. In fact, the overgrowth round the foramen magnum may be so great as almost to obliterate the cisterna magna. It is interesting to note in this connection that in some of the animals on these diets which show nerve defects, the pressure of the cerebro-spinal fluid is greatly increased and it may well be that it is the bone overgrowth round the foramen magnum which accounts for this abnormality. With the increased pressure the choroid plexus may be bunched up and its structure altered greatly.

More recently the investigation has been extended to the changes in the vertebral column and here again it is now possible to say that bone overgrowth takes place in that part of the vertebra where the nerves respectively enter and leave the spinal column, and there can be little doubt that pressure at these points may well cause the destructive changes in the nerves referred to.

If the nerve degenerative changes in peripheral nerves were due to bone pressure, as seems probable, the explanation of the curious differences between the afferent and efferent nerve roots of the spinal cord would also be satisfactory. Examined inside the spinal canal, the posterior roots showed much degeneration in these animals, and the anterior roots were free from degeneration. Since the actual overgrowth of bone affected these nerves as they left the spinal canal, the pressure on the nerves would destroy the afferent nerves centrally to the posterior ganglion but would leave the anterior root fibres central to the point of injury intact. On the peripheral side of the pressure, no doubt both afferent and efferent nerves were degenerated. The same explanation can probably be given of the normal appearance of the 7th nerve inside the skull. Pressure on this nerve also was applied by bone overgrowth at the base of the skull and in one case at least peripherally to this pressure the 7th nerve was degenerated, while centrally it escaped.

It may be added that the femur, radius and ribs of these animals are also affected and it seems probable that the whole osseous system is modified by this deficiency. As was originally pointed out, the new bone growth is very cancellous and contains many large marrow spaces, in contrast to the normal and more compact bone of animals receiving adequate vitamin A or carotene.

Adult dogs and rabbits fed on vitamin A deficient diets develop incoordination of movement and, at death, bone overgrowth is present. Adult dogs have been maintained on the deficient diet for periods of 9 to 14 months. Although definite bone overgrowth and some nerve degeneration have been seen, these have always been less in degree than those produced in the younger animals. It is probable that, with an increased experimental feeding period, the changes would become more pronounced. Adult rabbits, however, after a period of 8 to 12 months on diet show xerophthalmia, incoordination and, at death, bone overgrowth and nerve degeneration. The bone overgrowth in one of these adult rabbits showed, after 35 weeks of the vitamin A deficient diet, changes practically the same as those produced in a young animal after 16 weeks of the same deficient diet. It would therefore appear that the adult is susceptible to the deficiency described but that changes tend to be less severe and to take longer to produce than in the young growing animals.

There are still many difficulties to be cleared up before it can be accepted as certain that all the nerve degenerative changes produced by vitamin A deficiency are due to a primary overgrowth of bone causing pressure and stretching of the nerves. At the same time the evidence, in the case of some nerves at least, is very strong that such is the fact.

One of the main difficulties to be explained on this hypothesis is the degenerative change found in the second ascending neurones of the spinal cord, such for instance as those of the dorsal and ventral spino-cerebellar tracts. These fibres are probably the most affected of all in the experimental animals and it is not easy to see how pressure from bone can cause destruction of these endogenous fibres. It is difficult also to think that bone overgrowth can be responsible for some of the other well-known changes which follow vitamin A deficiency. Prior to the discovery of the bone overgrowth, I had already suggested that xerophthalmia is closely related to destructive changes in the Gasserian ganglion and fibres of the 5th nerve. This may well be the case, but it is not easy on this hypothesis to explain also night blindness which is caused by vitamin A deficiency and which is cured within a few hours of adding the vitamin to the diet. Even if the bone overgrowth changes are primary to nerve destruction, there is no indication yet how vitamin A deficiency can bring this about. In general, therefore, it can only be said that these observations are at such an elementary stage that it is impossible to indicate their significance.

It may be asked whether these results can be applied to the explanation of any clinical condition, and here again the answer must be that we do not know.

It will be seen from this survey of the subject of avitaminosis in relation to disorders of the nervous system that, important as have been the advances in knowledge of this subject, there is still a large field awaiting enquiry both from the experimental and clinical aspects.

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